

An Electrocardiographic Study of Cardiovascular
Problems in Mirex-Fed Rat Fetuses

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An Electrocardiographic Study of Cardiovascular Problems in Mirex-Fed Rat Fetuses

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ABSTRACT Sperm-positive female rats were intubated with pesticide, Mirex, in oil (5 to 10 mg/kg) on days 8½ to 15½. Controls were untreated or oil-fed. Testing was done on day 18½. Fetuses were sequentially exposed and ECGs obtained with the fetus attached to the placenta and uterus. Counterparts of standard leads, I, II and III were used. Fetuses were weighed and examined afterwards. Swollen fetuses were rated on a scale of 1 (slight edema under chin) to 5 (3 mm edema across back). ECGs from 81 controls and 205 Mirex fetuses were obtained. They were evaluated for rate of heart beat, regularity of beat, PR intervals, and other features. One control exhibited an abnormality, a transitory period of premature atrial contractions. Mirex-fed fetuses frequently exhibited tachycardia, closely correlated with degree of edema. The heart rate increased from 150/minute in controls to 180 in slightly swollen to 224 in swollen fetuses. Mean PR intervals increased with degree of swelling and with dose. The frequency of first degree heart-block was also dose-related, ranging from 20% in the 5 mg/kg group to 77% in the 10 mg/kg group. Second-degree heart-blocks were found in 8%, 3% showed arrhythmias, and one had atrial flutter/fibrillation. These cardiovascular problems seem primarily related to the Mirex-induced edema and demonstrate that fetal edema is not innocuous. These data demonstrate the usefulness of fetal electrocardiography to detect functional teratology.

The developmental toxicity of the pesticide Mirex (dodecachloro-octahydro-1,3,4-metheno-2H-cyclobuta (c,d) pentalene, also sold as a component of Ferriamicide), has been the subject of several studies. Gaines and Kimbrough ('70) reported a reduction in litter size in rats fed Mirex during gestation, and cataracts and a lowered viability in surviving neonates. Khara et al. ('76) found that feeding pregnant rats 1.5 to 12.5 mg/kg of Mirex on days 6 to 15 of gestation produced fetal death, skeletal and visual abnormalities, and fetal edema. Chernoff et al. ('79) fed pregnant rats 5 to 38 mg/kg of Mirex on days 7 to 16 and found increased fetal mortality, decreased weight, and a significant incidence of enlarged cerebral ventricles, undescended testicles and skeletal abnormalities. They also found a dose-related incidence of edematous fetuses, ranging from 6 to 75%.

Khara et al. ('76) did not attribute any significance to the edema. Chernoff et al. ('79) commented that some of the severely edematous fetuses were dead, but others had beating hearts and responded to tactile stimulation. Embryonic and fetal edema is induced by many agents which are also teratogenic in am-

phibia, birds, and several species of mammals including humans (Giroud et al., '55; Grabowski, '70, '77). Edema in the early stages of development has been traced to several types of abnormal development in a sequence of events termed the *edema syndrome* (Grabowski, '64, '70; Turbow, '66; Jaffee, '74). However, the consequences of edema during fetal stages are poorly understood. Mirex induces conspicuous edema in the later stages of development; therefore it seemed a good agent to use to study the effects of prolonged swelling on the fetus.

The initial phase of the Mirex study concentrated on the fetal heart since hypoxia induced edema in the 3-to-5-day chick embryo has been shown to induce hypervolemia, hypertension, and changes in the rate of heart beat (Grabowski and Schroeder, '68; Grabowski et al., '69). The primary technique used to study the heart was the fetal electrocardiogram. We have previously shown that anatomical and functional cardiac disorders could be prenatally detected with this method in rat

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fetuses exposed to Trypan blue (Grabowski and Tunstall, '77). Mirex-induced edema, in the present study, was found to be closely associated with a variety of cardiovascular problems, especially a high incidence of first and second degree heart blocks. The usefulness of the ECG method to supplement standard teratological techniques is demonstrated.

MATERIALS AND METHODS

Long-Evans rats obtained from the Blue Spruce Farms, Altamont, New York were used. Animals were maintained at $24^{\circ}\text{C} \pm 1^{\circ}$, 40 to 60% relative humidity, and on a 12-hour daylight period. They were housed in polypropylene cages on Sanicel bedding and fed Purina Lab Chow and water ad libitum. Virgin females in estrus, as determined by vaginal smear, were housed overnight with males and examined the following morning for the presence of sperm in the vagina. Rats were considered one-half day pregnant on the morning they were found to be sperm-positive.

The Mirex used was of commercial purity and was obtained from the Mississippi State Laboratory, Mississippi State University. It was dissolved in peanut oil and fed to the rats by gastric intubation. Treated rats were intubated daily with 5, 6, 7 or 10 mg/kg Mirex in 0.5 cc peanut oil. Initially animals were fed on days $6\frac{1}{2}$ to $15\frac{1}{2}$ of pregnancy. Later this was reduced to days $8\frac{1}{2}$ to $15\frac{1}{2}$ because we found this was just as effective as the longer treatment period. The doses for each rat were based on their weights on the day before the feeding regimen was started. Controls were given either no treatment or 0.5 cc plain peanut oil on days $8\frac{1}{2}$ to $15\frac{1}{2}$. Daily records of maternal weight and food and water intake were kept. All testing was done on day $18\frac{1}{2}$ of pregnancy.

Some preliminary results of these ECG studies have been published (Grabowski and Tunstall, '77; Grabowski, '78, '79), but since this is the first full report, the equipment and procedures are described in detail. The basic unit is a Tektronix 122 preamplifier powered with a Tektronix 125 Power Supply. The voltage gain on the preamplifier was set at $1000\times$, the high frequency response at 50 cycles, and low frequency response at 80 cycles. The electrodes consisted of about 15 mm of 0.007-inch pure silver wire soldered to the two leads of a miniature shielded cable (Fig. 1). The terminal portion of the shielding was twisted into a ground, to which another piece of silver wire was also soldered. The output of the preamplifier was monitored on an oscilloscope for con-



Fig. 1. An $18\frac{1}{2}$ day rat fetus in position for ECG recording. The electrodes are in position I. Note the umbilical cord (arrow) extending to the placenta, which is still attached to the uterus.

venience, but all measurements were made on permanent records obtained on a Brush 220 recorder. One mm of deviation on this instrument is equivalent to 1 mv at full sensitivity, but it was usually used at half of this value. The recorder delivers the chart at speeds of 1, 5, 25, and 125 mm/second with an accuracy $\pm 0.25\%$. The preamplifier, rat, and fetuses were kept in a galvanic cage which was kept warm (36°C) with an infra-red lamp placed overhead.

Various combinations of leads were tried, but the only ones routinely used in this particular study were comparable to leads I, II, and III of conventional human electrocardiography. These are, respectively, shoulder to shoulder, right shoulder to left thigh, and left shoulder to left thigh (Fig. 2). Electrodes were inserted into muscle to a depth of about 1 mm. The ground wire was inserted into the perineal area.

On day $18\frac{1}{2}$ of pregnancy the rats were anaesthetized with an IP injection of sodium pentobarbital, 30 mg/kg. Laparotomies were started about 15 minutes later. All further pro-

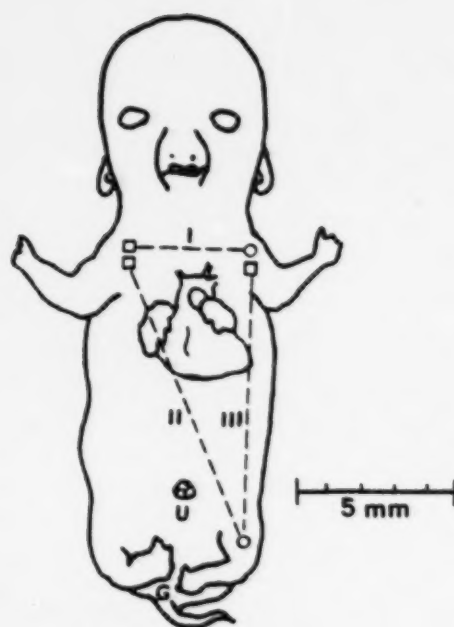


Fig. 2. Scale drawing of rat fetus of 18 $\frac{1}{4}$ days shown with drawing of the heart superimposed on the chest wall. The placement of the electrodes for positions I, II, and III are indicated. G, ground electrode placement; U, umbilicus; squares, positive electrode placement; circles, negative electrode placement.

cedures were timed beginning with the first incision. The fetuses were removed one at a time and placed into a shaped holder attached to a micromanipulator (Fig. 1). Placental attachment to the uterus was maintained and the umbilical cord arranged with minimal possible tension. This arrangement eliminates electrical noise due to maternal muscle movements. The cable, attached to another micromanipulator, was positioned over the fetus and the electrodes were inserted. The chart was first run at a speed of 5 mm/second to check the rate of heart beat. Recordings from leads I, II, III were successively made at 25 and 125 mm/second, and then the rate of heart beat was rechecked at 5 mm/second. The time required to prepare each fetus was 1 to 1 $\frac{1}{2}$ minutes. Tracings were taken for a period of about 1 $\frac{1}{2}$ minutes, sometimes longer if a problem was detected. It took about 20 to 30 minutes to check a full litter. Occasionally fetuses were rechecked in between litter mates or at the end of the session. Data from these were not used for the quantitative summaries because the rate of

heart beat slows down considerably after the fetus is detached from the uterus. All quantitative measurements were made from lead II tracings. This study is primarily based on an analysis of ECGs from 81 control fetuses and 205 Mirex-fed fetuses.

All fetuses were weighed at the conclusion of the recording session. They were then placed in a dish of saline and examined under a stereoscopic microscope for the presence of visible abnormalities and edema. Several ways to quantitate the edema were tried. Wet weights did not correlate well with edema because treated fetuses sometimes exhibited a moderate degree of growth retardation (see e.g., the wet weight data in Table 2). A good visual estimate of subcutaneous swelling could be made by examining immersed fetuses because the skin is very transparent at this stage. A rating system was adopted which ranked fetuses on a scale of 1 to 5, defined as follows:

- 0 - No edema apparent;
- 1° - slight swelling, mostly under chin;
- 2° - visible edema under chin, along belly and back;
- 3° - edema extends to head and upper arm, $\frac{1}{2}$ to 1 mm of edema visible across back;
- 4° - 1 $\frac{1}{2}$ to 2 mm of edema across back;
- 5° - 2 $\frac{1}{2}$ to 3 mm of edema across back.

Two operators independently rating the fetuses would agree in their estimates to within 0.5 degree. Later in the study, this scale was correlated with percent water determinations by taking a series of fetuses treated with from 5 to 7 mg of Mirex/kg body wt., rating them on the edema scale, obtaining wet weights and then drying at 70°C to constant weight.

Thoracic dissections were performed under a stereomicroscope on about half of the fetuses in both control and treated groups. Three fetuses, a control, a normal-appearing treated, and a swollen treated, were preserved in Bodian's solution, sectioned at 15 μ m and stained with Ehrlich's hematoxylin and Eosin.

Statistical significance was determined by the t-test.

RESULTS

Lethal and teratogenic effects of Mirex

The death rate was only slightly above normal in the 5 and 6 mg/kg groups but quite high in the 7 and 10 mg/kg groups (Table 1). Some treated fetuses appeared undersized and retarded. Seven fetuses (out of 205) were microphthalmic. No other externally visible abnormalities were noted.

TABLE 1. Lethal and teratogenic effects of Mirex treatment

Treatment	Number attempted	Maternal deaths	No. litters	Living fetuses	Resorptions	Microphthalmos
None	3	0	3	34	1	0
Oil only	5	0	4	47	5	
Mirex 5 mg/kg on days 6½ to 15½	2	0	2	23	1	0
on days 8½ to 15½	9	0	8	70	7	3
Mirex 6 mg/kg on days 8½ to 15½	8	0	6	60	7	3
Mirex 7 mg/kg on days 6½ to 15½	10	2	8	0	80	0
on days 8½ to 15½	11	2	9	49	33	0
Mirex 10 mg/kg on days 6½ to 15½	10	1	3	13	48	1

Mirex-induced edema

The degree of edema observed in 18½ day fetuses never reached the extremes observed in near term fetuses exposed to Mirex, when some individuals appear swollen to twice normal size (Khera et al., '76; Chernoff et al., '79). For the most part the edema observed would be considered slight and could be readily missed without careful examination under saline (Fig. 3). About half of the controls exhibited 1° edema, never more, but 85% of the treated fetuses were appreciably edematous. Half of the treated and control fetuses were dissected after ECG testing. There were no grossly discernible differences in the size of the thorax, abdomen, or viscera between normal and edematous fetuses. The edema seemed largely confined to subcutaneous layers. This was confirmed by examination of the serial sections. The edematous areas were extensive areas of very loose connective tissue, sometimes extending into and between the superficial musculature (Fig. 4).

As the investigation progressed, it became apparent that even a slight degree of edema could have a detectable physiological effect on the fetus. It became desirable to correlate the edema scale with total water determinations. The mean water content of 18½ day controls was 89.09% (Table 2). Edematous fetuses from Mirex-treated mothers showed regular increases to 89.77% water at 2° edema level, up to 91.17% at 4° level. The increments are not great, but this is not surprising since the controls are already 89% water. The difference between controls and treated fetuses with 1° edema was not significant, but that between



Fig. 3. A swollen 4° rat fetus, 18½ days, along with a normal appearing litter mate on the left. Both came from a mother who was fed 6 mg/kg Mirex per day. The subcutaneous edema in this photo is particularly evident across the forehead, chin and neck, and abdominal wall.

controls and with fetuses with 2°, 3°, and 4° edema was ($P < .001$). Similarly the difference between treated fetuses with 2° and 3° edema was also significant ($P < .001$) as was the difference between treated fetuses with 3° and 4° edema. In effect, the water content data of Table 2 represent a calibration of the edema scale.



Fig. 4. Cross section through the anterior thoracic wall of an edematous fetus. Note the loose, space-filled, subcutaneous connective tissue, even though considerable shrinkage of this region has taken place from the histological treatment. Note also that the edematous tissue extends between some of the superficial muscles.

TABLE 2. Wet weights and water content of 18½-day fetuses

	No.	Wet weight Mean $\pm$ SEM	% H ₂ O Mean $\pm$ SEM
Controls	23	1.320g $\pm$.015	89.09 $\pm$.096
Treated, 1° Edema	3	1.373 $\pm$.065	89.53 $\pm$.353
Treated, 2° Edema	39	1.242 $\pm$.034	89.77 ² $\pm$.087
Treated, 3° Edema	31	1.278 $\pm$.033	90.52 ² $\pm$.108
Treated, 4° Edema	30	1.357 $\pm$.030	91.17 ² $\pm$.088

¹Treated with Mirex, 5 to 7 mg/kg/day on days 8½ to 15½ of gestation.

²Significantly higher than controls ($P < .001$). The increments between 2°-3° and 3°-4° were also significant ($P < .001$).

Characteristics of the ECG of normal rat fetuses

The ECG of the 18½ day rat fetus is mature and clearly shows P, QRS, and T components. The tracings look somewhat different from those of the human adult, presumably because of the small size of the heart and the fact that

the electrodes are placed very close to it (Fig. 2). The QRS interval in adult humans is about 0.08 seconds versus 0.02 seconds in the rat fetus. Consequently the individual components cannot always be easily visualized at a chart speed of 25 mm/second, which is the standard clinical rate. The record for every fetus contains segments run at 3 different speeds, 5, 25, and 125 mm/second. Records obtained at the 5 mm/second rate are convenient for measuring rate of heart beat and visualizing arrhythmias (Fig. 7a). Those at the 25 mm/second rate are good for visualizing the T wave and for detecting some abnormalities (Fig. 7b). Records obtained at the 125 mm/second rate are the only ones in which the P and QRS complexes are sufficiently spread out to be examined with clarity (Fig. 7c).

The rate of heart beat was obtained from the ECG records taken as soon as possible after the fetus was exposed and at the conclusion of the recording session. The heart rate usually starts to slow down gradually after fetal exposure, but sometimes remains constant or even speeds up slightly. The before and after measurement of heart rate almost always

agreed within $\pm 10\%$. The mean rate of heart beat of 18½ day fetuses (untreated controls) was 149 ± 4.95 (SEM) beats per minute.

The ECGs obtained from 81 control fetuses of this study were normal with but a single exception. One untreated control fetus developed a transient episode of premature atrial contractions, most of which were blocked. The abnormality started 30 seconds after recording was started. Two minutes later the beat returned to normal. This fetus was rechecked 10, 20, and 40 minutes after being removed from the mother. The rate of beat was reduced at these times, but the beat was regular and ECG normal. This particular abnormality was not found in any treated fetus of this series. It was also the only abnormality found in over 300 ECGs of control fetuses taken in this and other experimental series.

ECGs of Mirex-treated fetuses

Edema and the rate of heart beat. The heart rate in treated fetuses was more rapid than normal and this increase was related to the degree of visible edema (Fig. 5). The mean rate in both treated and untreated controls is 150 beats/minute. It jumps to 181 beats/minute in the slightly swollen (2°) and 224 beats/minute in the grossly swollen (4°) treated fetuses. There was a drop in mean rate of heart beat in severely swollen fetuses (5°) due to a very low rate (down to 144 beats/minute) in a few individuals. All the differences in the rates of heart beat between fetuses with 1° edema or higher and treated controls were significant ($P < .001$), but that between treated fetuses without visible edema and controls was not.

First degree heart block in treated fetuses. The PR interval in normal humans varies somewhat with age and rate of heart beat. The range for newborns is 0.07 to 0.14 seconds with an average of 0.11 seconds (Schaffer and Avery, '77). The range for adults is 0.14 to 0.18 seconds (Litman, '72). A prolongation of the PR intervals beyond 0.20 seconds in adults usually indicates a delay in impulse conduction from the sinus node to the ventricles and is called a first degree heart block.

The mean PR interval in untreated control rat fetuses was $.069 \pm .008$ (SD) seconds and in oil-fed controls was $.065 \pm .006$ seconds. The difference between the two is probably due to subtle improvements in technique as the study progressed. The mean PR interval of all controls was $.067 \pm .007$ seconds, about 8 mm on the records taken at a chart speed of 125 mm/second (Fig. 7c). A first degree heart block in

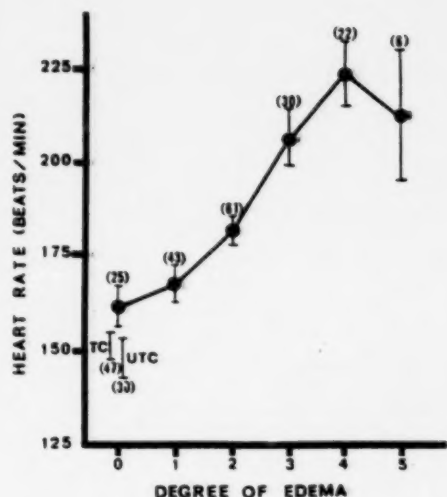


Fig. 5. The rate of heartbeat (mean $\pm$ SEM) in Mirex-treated fetuses with different degrees of edema. Sample sizes are in parentheses. TC, Treated controls; UTC, Untreated controls.

18½ day rat fetuses was defined as any PR interval greater than the mean interval in controls (.067 seconds) plus three standard deviation intervals (.021 seconds), i.e., 0.088 seconds. This is a convenient interval to measure because it is 11 mm on the 125 mm/second records.

The PR interval in Mirex-treated fetuses was considerably more variable than that of controls. Though in many of them the PR interval fell within the normal range, in others it was prolonged (Figs. 8 and 9), sometimes up to 3½ times normal. First degree heart blocks, using the criterion defined above, were common and related to both dose and degree of edema. The frequency of first degree heart block ranged from 20% in the 5 mg/kg group to 77% in the 10 mg/kg group (Table 3). An increase in mean PR interval was also dose-related (Table 3). There was a proportional relationship between PR intervals and the degree of edema present in the fetuses (Fig. 6). The differences between the mean PR intervals of the ECGs of all edematous fetuses (1° through 5°) were significantly greater ($P < .001$) than those of oil-fed controls.

Second degree heart blocks and other abnormalities. Some of the first degree heart blocks led to a second degree block, in which some atrial contractions were not followed by

TABLE 3. PR intervals and heart block in Mirex-fed rat fetuses

	Number	Mean PR interval in seconds $\pm$ SEM	1° heart block	2° heart block
Untreated Controls	34	.069 $\pm$.0014		
Treated Controls	47	.065 $\pm$.0009		
5 mg Mirex	93	.079 $\pm$.0019	20%	4%
6 mg Mirex	60	.091 $\pm$.0023	50%	10%
7 mg Mirex	49	.086 $\pm$.0036	27%	4%
10 mg Mirex	13	.110 $\pm$.0069	77%	8%

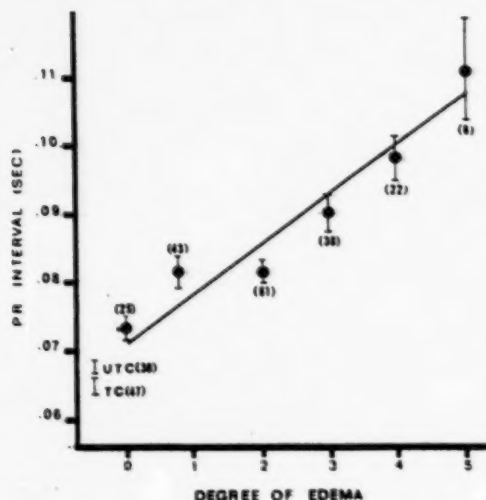


Fig. 6. Mean PR intervals ($\pm$ SEM) in the ECG's of Mirex-treated fetuses with different degrees of edema. Sample sizes are in parentheses.

ventricular contractions. This cardiac problem occurred in from 4 to 10% of the groups of Mirex-treated fetuses. All of the cases of second degree heart blocks were Type I (Wenckebach), in which the missing beat is preceded by progressively longer PR intervals (Fig. 9). Fetuses with second degree heart blocks were often rechecked for periods of up to 20 minutes after being removed from the uterus. The irregularities inevitably persisted.

A single case of atrial flutter or fibrillation was found in one of the 8 severely swollen (5°) fetuses (Fig. 10). Several kinds of arrhythmias, presumably pacemaker problems, were found in the ECGs of 5 individuals scattered through the dosage groups (Fig. 11a and b).

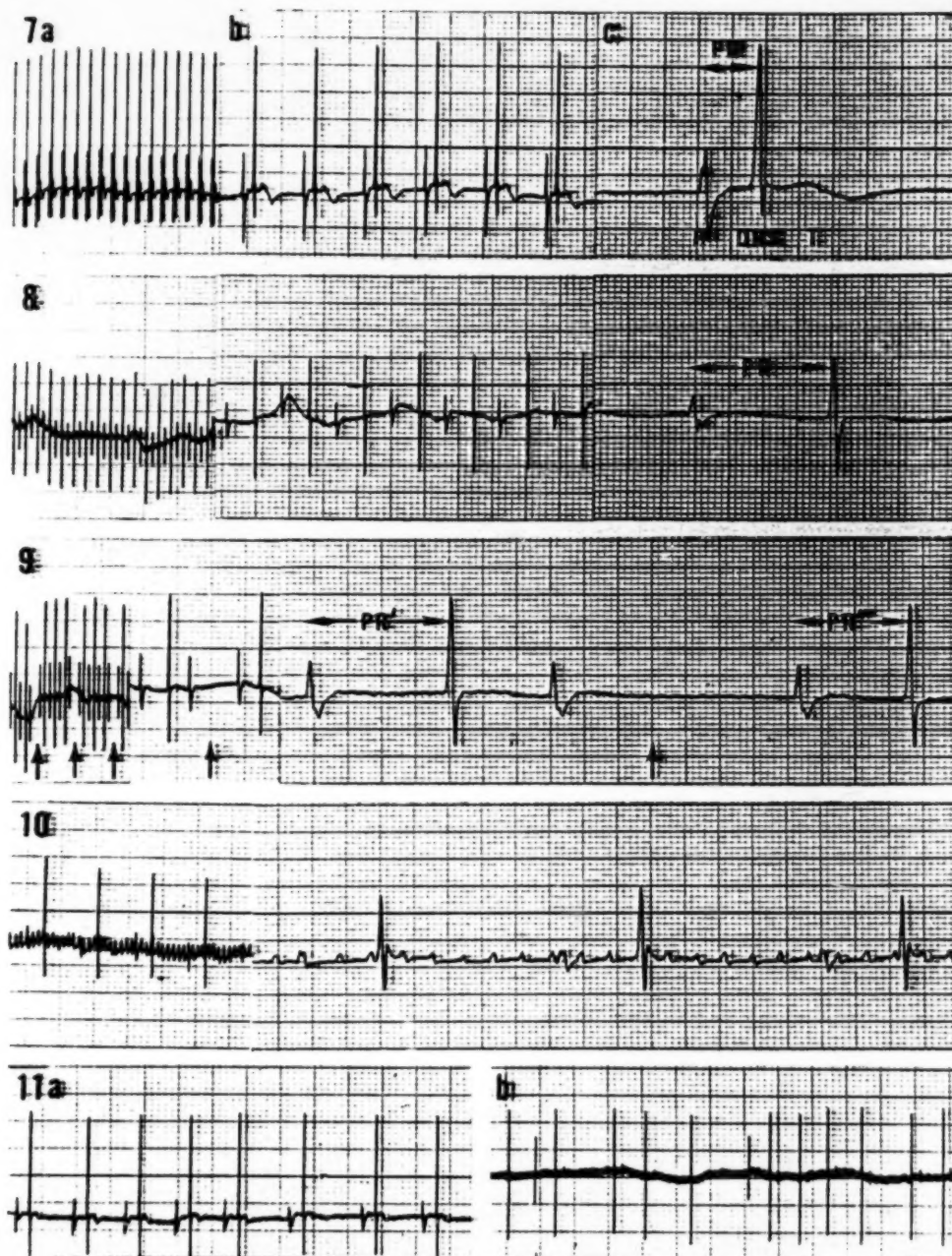
Morphological observations. No gross differences were apparent in the size and proportion of the thoracic cavity in the dissected fetuses of treated and control groups. There were no grossly visible differences in the appearance of the heart. The serial sections through the control and two treated fetuses did not show any obvious differences between their hearts.

DISCUSSION

Mirex toxicity

The developmental toxicity of Mirex fed to pregnant rats has been well documented (Gaines and Kimbrough, '70; Khara et al. '76; and Chernoff et al., '79). Lowered prenatal and postnatal viability, prenatal edema, as well as a few anatomical abnormalities have been reported. Mirex-induced microphthalmos (4% in this study) had not been observed before. The major new observations of this study have been 1) a description of the Mirex-induced cardiovascular changes, and 2) a quantitation of the occurrence of edema. The scale of edema ratings, which fortuitously was adopted early in the study, eventually made feasible a number of correlations between edema and other problems. The maximum amount of edema which we observed in 18½ day fetuses was never as extreme as that shown by Chernoff et al. ('79). This is due to the fact that the latter made their observations on the 20th day of gestation. We have noted a much higher incidence of edematous fetuses than either Khara et al. ('76) or Chernoff et al. ('79), even though our dosage was in the moderate range. This probably reflects our emphasis on edema as well as methods of observations.

In addition to the edema, several kinds of cardiovascular problems were detected in Mirex-fed fetuses. Some of these, such as the arrhythmias, are probably benign. Others,



such as 2° heart block and atrial flutter/fibrillation, are more serious and apparently are responsible for some fetal deaths (Grabowski, '79). These cardiovascular disturbances appear to be a significant facet of Mirex toxicity in the prenatal period.

The physiological basis for the Mirex-induced cardiovascular changes

The most prominent cardiovascular symptoms observed were tachycardia and first and second degree heart blocks. It is difficult to ascribe a possible cause to these symptoms on the basis of human pathology. Among the many causes of tachycardia which could possibly be operative in this situation are anoxia, hypotension, and cardiac failure (Marriott and Myerburg, '79). There is no reason to suspect the first two, but the latter is a possibility. Chernoff et al. ('79) observed enlarged cerebral ventricles in Mirex-fed fetuses, and this could possibly result in increased intracranial pressure. However, increased intracranial pressure leads to bradycardia in adults rather than tachycardia. The list of agents which can induce heart blocks is also long and includes vagal stimulation, anoxia, ischemic heart disease, and hyperkalemia (Marriott and Myerburg, '70). Though rat fetuses are very susceptible to hyperkalemia, especially after exposure to hypoxia, (Chernoff and Grabowski, '71; Grabowski, '73), we have found only a slight elevation in serum potassium in Mirex-treated fetuses ($5.1 \text{ mEq/l} \pm 1.4$ in 18½ day controls; 6.2 ± 1.6 in treated). The blood of Mirex-treated fetuses at 20½ days has only a very slightly

lower P_{O_2} than that of controls, 142 vs 152 mm respectively (Grabowski, '80). These observations would seem to eliminate either hyperkalemia or anoxia as possible explanations of the cardiovascular changes. Measurements of fetal blood pressure and blood volume will be necessary to decide between the remaining alternatives. Such studies are underway. The only clue available at the moment is that the correlation between the degree of visible edema observed and degree of tachycardia and prolonged PR intervals is too close to be totally spurious.

Prenatal edema and its consequences

Mirex was the primary subject of this investigation, but also, this was a study of fetal edema and its physiological effects. Embryonic and fetal edema can be induced by numerous agents in several groups of vertebrates as well as by genetic factors. Edema in the embryonic stage can have lethal and teratogenic effects due either to the distention of hollow organs during a critical period of development or to the mechanical effects of persistent hematomas near or within developing structures (Jost, '53; Giroud et al., '55; Grabowski, '70, '77; Jaffee, '74).

The significance of edema produced in the fetal stages is, in contrast, poorly understood and usually dismissed without comment. The present study shows that fetal edema is associated with significant cardiovascular effects. The enlarged cerebral ventricles in Mirex-fed fetuses (Chernoff et al., '79) are probably another manifestation of fetal edema. Such en-

Fig. 7. Electrocardiogram of a normal 18½ day rat fetus, taken at chart speeds of (a) 5 mm/sec, (b) 25 mm/sec., and (c) 125 mm/sec. The rate of heart beat was 172/minute. The P, QRS, and T components are labeled in 7c, along with the PR interval (.064 second). Actual size.

Fig. 8. Electrocardiogram of a Mirex-treated fetus (5 mg/kg per day) showing a pronounced first degree heart block. Note the extremely long PR interval (0.16 second). Segments of the 5, 25, and 125 mm/second record are shown. The waviness in the base line is due to drift in the amplifier. Edema 2°. Heart rate 168/minute.

Fig. 9. Electrocardiogram of a Mirex-treated fetus (6 mg/kg per day) showing a second degree heart block. The missing QRS complexes are indicated by arrows. Note that the two PR intervals, PR' PR", are of different duration. Edema 4°. Heart rate 210/minute. Segments of the 5, 25, 125 mm/second record are shown.

Fig. 10. Electrocardiogram of a Mirex-treated fetus (6 mg/kg) with either atrial flutter or fibrillation. The P waves are occurring at a rate of 36/second. Edema 5°. Heart rate 204/minute. Segments of the 25 and 125 mm/second record are shown.

Fig. 11. Electrocardiograms of two treated fetuses with arrhythmia. (a) A mild irregularity in a fetus exposed to 6 mg/kg/day. Note the varied intervals between successive QRS waves. Edema 2°. Heart rate 228. Chart speed 25 mm/second (b) A very irregular beat due to an arrhythmia along with a second degree heart block in a fetus exposed to 10 mg/kg/day. Edema 5°. Heart rate 120. Chart speed 5 mm/second. These ECG's illustrate the variety of conditions detectable by this method.

largements could affect the function of the central nervous system. Other hollow organs could be similarly affected. Posner and Darr ('70) have suggested that the edema induced by the antihistamine chlorcyclizine is responsible for the high incidence of cleft palate produced by this agent because the swelling of facial tissues interferes with their morphogenetic movements.

Fetal edema in mammals is not uncommon. Some of the agents which induce conspicuous edema include chlorcyclizine (King et al., '65), thalidomide (Khera, '75), clamping of uterine blood vessels (Leist and Grauwiler, '74), and carbon monoxide and vasopressin (Grabowski, unpublished). It is occasionally observed in human babies (Potter, '61; Schaffer and Avery, '77). Studies on the physical and chemical properties of fetal blood are under way which may help understand why mammalian fetuses are susceptible to this type of fluid disturbance.

The potential of fetal electrocardiography in developmental toxicity studies

The domain of teratology has been enlarged in recent years to include functional as well as anatomical disorders induced by various environmental factors (Wilson, '73). Suitable procedures for the systematic detection and evaluation of functional disorders in experimental animals are not, as yet, common. Fetal electrocardiography could become a relatively simple, standardized procedure for detecting functional disorders of the cardiovascular system. Numerous specific disorders can be detected and measurements of the rate of heart beat, whether feeble or excessive, could give some indication of the general state of health of the fetus. It can also be applied to newborns (Grabowski, '79). The ECG equipment required is neither expensive nor esoteric. The skill required is not beyond the reach of a good technician. A litter can be tested in about half an hour, and the individuals could still be subsequently used for necropsy or skeletal analysis. This method could be a valuable adjunct to traditional procedures.

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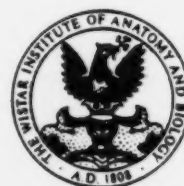
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